UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,572	07/11/2001	Takashi Okuda	010898	4818

23850 7590 10/20/2003

ARMSTRONG, KRATZ, QUINTOS, HANSON & BROOKS, LLP
1725 K STREET, NW
SUITE 1000
WASHINGTON, DC 20006

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	20

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,572	OKUDA ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I and subinvention (B) in Paper No. 17 is acknowledged. Claims 1-18, and 20 are pending and under consideration to the extent that they read on DNAs (and compositions thereof) comprising at least one substitution of an Asparaginine in an NXB N-glycosylation site for another amino acid.

2. Claim 19 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 17.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on October 24, 2001, and June 19, 2003, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

4. The IDS filed on May 9, 2003 has not been separately considered as the June 2003 IDS was a corrected version of the same reference listing.

5. The Yoshida et al. reference (reference AK) of the October 2001 IDS has been crossed out on that IDS as the reference has was also considered as part of the June 2003 IDS.

6. It is noted that the Suzuki et al reference of the October 2001 reference (U.S. Patent 5,484,970) does not appear relevant to the presently claimed invention. If the Applicant desires

to point out any particular teaching of the reference for consideration, they are invited to do so in Response to this action.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-18, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on DNA molecules "derived from" prokaryotic cells. It is not clear what the term derived from is intended to convey. For example, Narhi et al. (Prot Engineer 14: 135-40, Nahri I) teaches an erythropoietin (EPO) gene derived from E coli. Page 135. However, it also appears that the EPO gene was recombinantly inserted in the E. coli cells. See e.g. Narhi I, page 135 (first text paragraph referring to EPO expressed in E. coli, and citing Nahri II); and Nahri et al., J Biol Chem 266: 23022-26, page 23022 (teaching the expression of human EPO in E. coli). Because the Applicant has not provided a definition for the term "derived from," and because the term could equally be applied to non-prokaryotic genes isolated from prokaryotic cells and prokaryotic genes, it is unclear from the application what DNAs are included by the claim language "DNA molecules derived from a prokaryotic cells."

9. Claims 1-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is treated as representative of the rejected claims.

This claim describes a DNA encoding NXB. The term NXB is followed by a parenthetical statement. It is unclear if the parenthetical statement is an identification of, or an example of, NXB. It is suggested that the claims be amended such that the independent claims include not a parenthetical identification, but a statement such as –encoding a potential NXB N-glycosylation site, wherein N is asparaginine, X is any amino acid other than proline, and B is either serine it threonine--. Clarification of the relationship between the parenthetical and the term NXB would avoid the rejection.

10. Claims 1-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is treated as representative of the rejected claims. This claim describes a DNA derived from a prokaryotic cell, the DNA comprising a modification in a NXB N-glycosylation site such that no such glycosylation occurs when expressed in a eukaryotic cell. It is unclear if the N-glycosylation being prevented is the N-glycosylation of the entire protein, or N-glycosylation of the specific NXB site that has been modified.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-3, 6, and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Liu et al., Prot Exp and Pur 19: 304-11 (of record in the June 2003 IDS). Claims 1-3 claim read on DNA molecules encoding antigenic proteins derived from prokaryotic cells wherein the DNA has been modified as described above. Claims 6 and 7 further limit the claims DNAs to embodiments wherein the DNAs encode a fusion protein of the prokaryotic proteins and a leader sequence from another protein. Liu teaches the making and use of such a protein through site-specific mutation of the prokaryotic protein. Page 306. The DNA is further disclosed as encoding a mammalian signal sequence. Page 305. The reference therefore anticipates the identified claims.

13. Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Narhi I (supra). The claims have been described above. The teachings of Narhi et al., have also been, in part, described above. The reference further teaches that the EPO gene derived from E. coli (a prokaryotic cell) was modified such that the asparaginine residues at positions 24, 38, and 83 were substituted with a lysine. Abstract. These are all asparaginines in known EPO NXB sites. See, Lai et al., J Biol Chem 261: 3116-21 at 3116, last paragraph. Further, as antibodies against the protein have been raised in mice, it is apparent that the protein is antigenic. See, Sytkowski et al., J Biol Chem 260: 14727-31, at 14729. Thus, the reference teaches DNAs as described in the identified claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-3, 6, 7, 10, 11, 13, 15-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Jacobson et al. (U.S. Patent 5,656,485), or Saitoh et al. (U.S. Patent 5,871,742- of record in the October 2001 IDS) in view of the teachings of Marini et al. (Mol Microbiol 38: 552-64), Essex et al. (U.S. Patent 6,103,238- of record in the June 2003 IDS), and Liu et al. (Prot Exp and Pur, supra), and further in view of the teachings of R. Parekh (Curr Opin Biotech 2: 730-34). Each of Jacobson and Saitoh teach the use of viruses comprising DNA encoding antigenic proteins to infect eukaryotic cells to express the proteins. Jacobson, Cols 3-4, and 15, lines 25-36; and Saitoh, abstract. Further, each of the two patents teaches that the antigen may be expressed as a fusion protein with a signal or a signal anchor peptide such that the antigen will be secreted or anchored to the cell surface. Jacobson, col 4, lines 7-20; and Saitoh, cols 4-5. Thus, it would have been obvious to those in the art to construct DNAs encoding prokaryotic antigen proteins, including such wherein the antigen is expressed as a fusion with an N-terminal signal peptide. However, the references do not teach the modification of an NXB site.

Parekh teach that eukaryotic cells have processes for protein N-glycosylation that are not found in prokaryotic cells. Parekh, page 730. Thus, the reference puts those in the art on notice as to a potential problem with expressing proteins in eukaryotic cells. However, each of the

references of Liu, Essex, and Marini teach that such N-glycosylation may be avoided by modification of the NXB sites by substituting another amino acid for the asparaginine. Thus, it would have been obvious to those in the art to use the protein expression methods taught by Saitoh or Jacobson for the expression of prokaryotic antigens. It would also have been obvious to modify the DNAs used in those methods such that the prokaryotic proteins would not be glycosylated in the eukaryotic systems. Further, it was known in the art that preventing glycosylation of protein antigens generally may increase the antigenic properties of the proteins. See e.g., Essex et al., U.S. Patent 6103,238, abstract (teaching the improvement of HIV gp120 by modification of NXB glycosylation sites,). Thus, there is motivation for those in the art to modify prokaryotic genes for expression in eukaryotic cells.

Those in the art would have also had a reasonable expectation of success in the making of such DNAs and vectors because those in the art knew of the potential effects of modifying the proteins. For example, the Marini reference indicates that those in the art were aware of the potential effects on protein function by such modification. See, pages 555-57 (teaching that the Marini authors tested the modified protein for effects on the protein activity). See also, Narhi I, supra, abstract, and page 140 (indicating that the authors, in making the substitutions, were aware of the potential modifications to protein activity and structure, and took precautions to ensure that the desired protein activity would not be affected). Thus, in view of the teachings of the references above, it would have been obvious to those in the art to construct DNAs, and viral vectors comprising such, for the expression of prokaryotic antigens, and to modify such DNAs such that the could be expressed in eukaryotic cells without being subject to the N-glycosylation of NXB sites that occurs therein.

16. Claims 8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobson, Saitoh, Liu, Essex, Marini, and Parekh as applied to claims 1-3, 6, 7, 10, 11, 13, 15-18 and 20 above, and further in view of Nippon Zeon Co., LTD. (EP 0905140- Nippon). Claims 8 and 14 further limit the DNAs and viral vectors as described above to embodiments wherein the signal sequence is from either the gB gene of Marek's Disease Virus (MDV), or the gG gene of Rabies virus. The teachings of the references other than Nippon have been described above. Those references do not disclose the use of either of the two claimed signal sequences in the DNA. However, Nippon, which teaches the use of an expression system similar to that in Saitoh, teaches signal sequences from the gB protein of MDV that can be used in a fusion protein for the expression of a prokaryotic antigen. Thus, it would have been obvious to use such a signal sequence in the method indicated by the references cited above.

Examiner's Note

17. No art rejection is being made over claims 4, 5, 9, or 12 at this time. These claims read on modifies DNAs from a prokaryotic cell, wherein the prokaryotic cell is a Mycoplasma. Particularly wherein the DNA encodes the MGC3 protein. As indicated above, it is obvious to those in the art to modify prokaryotic DNAs as claimed for expression in eukaryotic cells. Further, Mycoplasma antigens, including the MGC3 protein are known in the art. See e.g., Saito et al., EP 0905140 (of record in the June 2003 IDS); and Yoshida et al., Infect and Immun 68: 3186-92 (also cited in the June 2003 IDS). However, while the art teaches both the claimed DNA modification, and the claimed prokaryotic antigen, there is no suggestion in the art to modify the

mgc3 gene as claimed. This because, while the art indicates that certain benefits may be obtained by preventing N-glycosylation of proteins expressed in eukaryotic host cells (e.g. by NXB modification), each of Yoshida and Saito indicates that the Mycoplasma proteins expressed in eukaryotic cells were antigenic without such modification. Thus, the art provides no motivation for the modification of genes encoding the Mycoplasma antigens.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

James C. Housel 10/18/03

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600